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Effect of carbazochrome sodium sulfonate combined with tranexamic acid on blood loss and inflammatory response in patients undergoing total hip arthroplasty

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Aims

The purpose of this study was to examine the efficacy and safety of carbazochrome sodium sulfonate (CSS) combined with tranexamic acid (TXA) on blood loss and inflammatory responses after primary total hip arthroplasty (THA), and to investigate the influence of different administration methods of CSS on perioperative blood loss during THA.

Methods

This study is a randomized controlled trial involving 200 patients undergoing primary unilateral THA. A total of 200 patients treated with intravenous TXA were randomly assigned to group A (combined intravenous and topical CSS), group B (topical CSS), group C (intravenous CSS), or group D (placebo).

Results

Mean total blood loss (TBL) in groups A (605.0 ml (SD 235.9)), B (790.9 ml (SD 280.7)), and C (844.8 ml (SD 248.1)) were lower than in group D (1,064.9 ml (SD 318.3), $p < 0.001$). We also found that compared with group D, biomarker level of inflammation, transfusion rate, pain score, and hip range of motion at discharge in groups A, B, and C were significantly improved. There were no differences among the four groups in terms of intraoperative blood loss (IBL), intramuscular venous thrombosis (IMVT), and length of hospital stay (LOS).

Conclusion

The combined application of CSS and TXA is more effective than TXA alone in reducing perioperative blood loss and transfusion rates, inflammatory response, and postoperative hip pain, results in better early hip flexion following THA, and did not increase the associated venous thromboembolism (VTE) events. Intravenous combined with topical injection of CSS was superior to intravenous or topical injection of CSS alone in reducing perioperative blood loss.

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Keywords: Blood loss, Tranexamic acid, Carbazochrome sodium sulfonate, Transfusion, Total hip arthroplasty

Article focus

- The purpose of this study was to investigate the effects of carbazochrome sodium sulfonate (CSS) combined with tranexamic acid (TXA) on blood loss, inflammation, and thromboembolic complications, and to investigate the influence of different administration methods of CSS on perioperative blood loss during total hip arthroplasty (THA).

Key messages

- TXA combined with CSS had lower total and hidden blood loss than TXA alone.
- TXA combined with CSS had lower levels of inflammatory biomarkers (CRP,

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interleukin-6, ESR) and pain scores, and better hip range of motion than TXA alone.
- CSS combined with TXA did not increase the associated VTE events.

Strengths and limitations

- This is the first study to evaluate perioperative haemostasis and anti-inflammatory effects using CSS combined with TXA in patients undergoing THA.
- The survival and fixation of joint prostheses were not investigated in this study.

Introduction

Although a large number of studies have shown that tranexamic acid (TXA) could effectively reduce perioperative blood loss in total hip arthroplasty (THA), some patients still receive blood transfusions during or after the operation.[1-5] Furthermore, TXA is not only an effective anti-fibrinolytic agent, but also has some anti-inflammatory effects.[6,7] Studies have also shown that TXA could significantly reduce intraoperative blood loss and transfusion rates, but not hidden blood loss (HBL).[8-11] Therefore, it is necessary to reduce HBL after THA in order to speed up patients' postoperative recovery.

Carbazochrome sodium sulfonate (CSS) can be used to treat bleeding due to its ability to increase capillary permeability and enhance the contraction of broken ends of capillaries.[12,13] Although the mechanism of action is still unclear, recent studies have shown that it could reverse thrombin-, trypsin-, and bradykinin-induced increase of endothelial cell permeability by reducing the formation of intracellular actin stress fibres and restoring tight cellular connectivity.[14,15] Furthermore, CSS is also used in urology, otolaryngology, etc., and studies have shown that CSS can improve symptoms of nose bleeding as well as pain and post-urination symptoms in patients with refractory chronic prostatitis.[16,17] Furthermore, one study showed that TXA combined with CSS had significantly reduced blood loss after total knee arthroplasty without increasing the risk of thromboembolism complications.[18] Therefore, we speculated that the use of CSS combined with TXA during and following THA could reduce perioperative blood loss, transfusion rate, and inflammatory reaction, and accelerate postoperative recovery without the occurrence of thromboembolic complications. The purpose of this study was to examine the efficacy and safety of CSS combined with TXA on blood loss and inflammatory responses after primary THA.

Methods

Patients and design. This trial was ethically approved by our Institutional Review Board and registered with the Chinese Clinical Trial Registry (ChiCTR1800020094) in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[19] Informed consent was provided before the surgery by all patients to participate in the study.

All patients diagnosed with hip osteoarthritis or femoral head necrosis, and scheduled for unilateral primary THA between December 2018 and March 2019, were eligible for inclusion in this trial. Patients with a history of renal failure, arterial thromboembolism (e.g. myocardial infarction or stroke), arterial stenting, deep-vein thrombosis (DVT), or pulmonary embolism (PE), revision surgery, and low haemoglobin levels (< 110 g/l) were excluded. We also excluded patients with allergies to TXA, CSS, and patients who refused to participate in the study or agree to receive blood products. We also excluded patients with a BMI greater than 35 kg/m^2.

Study medication regimen. Enrolled patients were randomly assigned into four groups using a computer-generated randomization protocol. The dedicated study nurse prepared the study drugs and placebo (a powder identical in appearance to the study drugs) to ensure blinding. One of two experienced surgeons (PK) registered the patients and a professional assistant (ZY) reviewed the inclusion criteria and recorded the basic details. All the patients, surgeons, and researchers involved in the treatment were unaware of the distribution of the study group throughout the study period. All four groups received 1,000 mg of TXA (intravenous) just before skin incision.[20] Group A was injected with 40 mg CSS (Luo Ye, Wuzhong Pharmaceutical Group, China) around the joint capsule before closure, and 60 mg CSS was injected intravenously three hours after the surgery. Group B was given the same treatment as group A, but placebo was given three hours after the operation. In group C, placebo was injected intraoperatively around the joint capsule, and 60 mg of CSS was injected intravenously three hours after surgery. Group D was given the placebo during operation and three hours postoperatively. No patients used the drainage tube after the operation.

Surgical technique and perioperative management. All THAs were performed under general anaesthesia by a surgical team consisting of a senior surgeon (PK) and two fellows via the posterolateral approach. The same cementless acetabular (Pinnacle acetabular component; Depuy Synthes, USA) and femoral components (Corail stem; Depuy Synthes) were used in all procedures. Blood transfusion was required when haemoglobin concentration was less than 70 g/l or 70 to 100 g/l with symptoms of anaemia, such as mental disorders or palpitations. After returning from the operating room to the ward, the patients began ankle-pumping and knee-stretching exercises. Low molecular weight heparin ((LMWH) 0.2 ml, or 2,000 IU aXa; Clexane, France) was first given 12 hours after the operation, followed by daily use of 0.4 ml until hospital discharge. After discharge, 10 mg of rivaroxaban was prescribed daily for ten days to prevent venous thromboembolism (VTE). If there were perioperative symptoms associated with DVT, an ultrasound scan was performed immediately. Doppler ultrasound was routinely used to detect DVT before surgery, two weeks

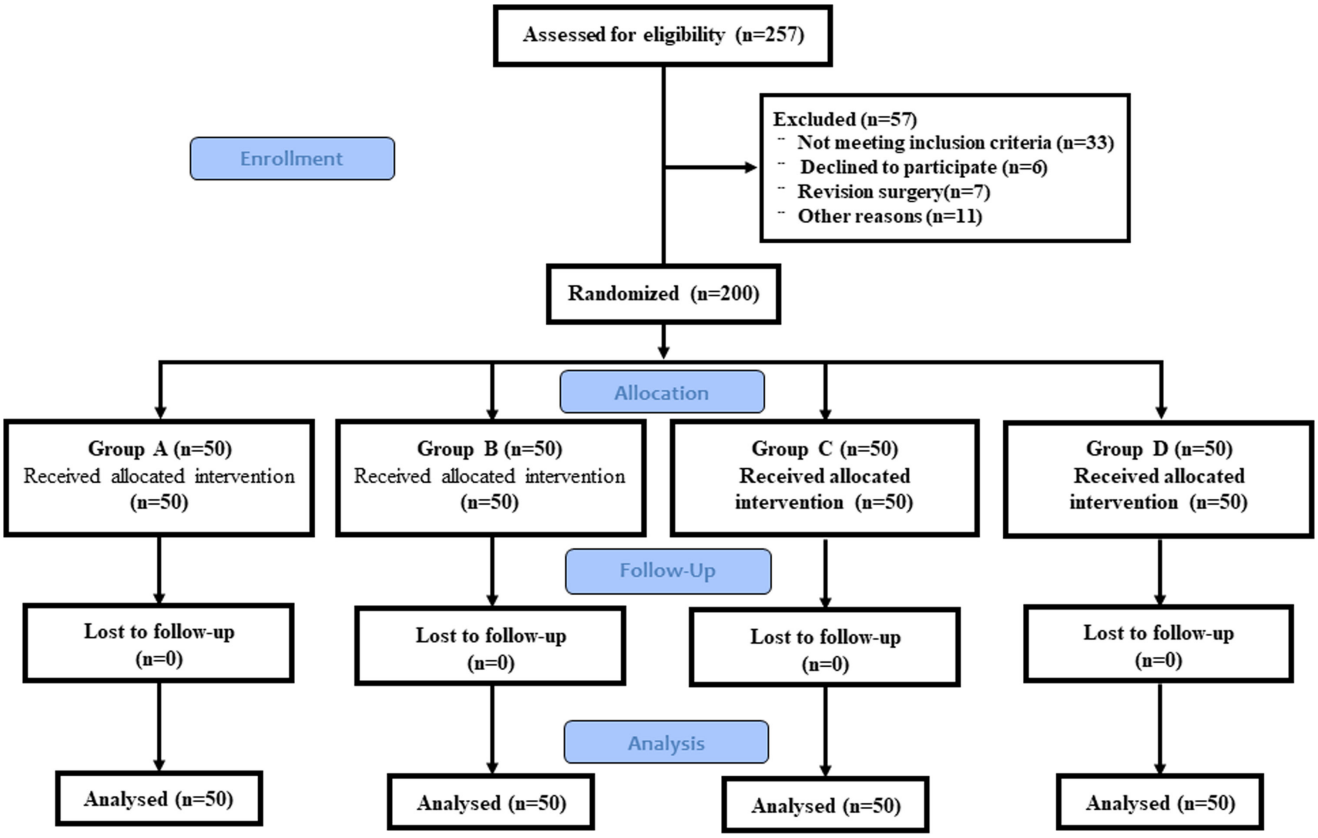

Fig. 1

Flow diagram showing participant screening and allocation. Group A received tranexamic acid (TXA) plus topical and intravenous carbazochrome sodium sulfonate (CSS); group B received TXA plus topical CSS only; group C received TXA plus intravenous CSS only; and group D received TXA only.

after surgery, and one and three months after surgery. If the patient was suspected to have PE-related symptoms, then enhanced CT examination was performed.

Outcome measures. The primary outcome measure was total blood loss (TBL), which was calculated according to a formula by Gross and Nadler et al.[21–23] Secondary outcome measures included hidden blood loss (HBL), reduction in haemoglobin (Hb), intraoperative blood loss (IBL), transfusion rates, inflammatory marker levels, perioperative visual analogue scale (VAS) pain score, length of hospital stay (LOS), range of hip motion at discharge, operating time, and Harris Hip Score (HHS)[24] preoperatively, and at the three-month postoperative follow-up, transfusion rate and incidence of VTE and other complications. HBL was defined as the TBL minus IBL.[25–27] IBL was calculated by measuring suction drain contents and weighing gauzes. The reduction of Hb level was calculated as preoperative Hb level minus postoperative minimum Hb level.

TBL was calculated as previously described:[21–23] TBL = patient's blood volume (PBV) × (Hctpre–Hctpost)/Hctave, where Hctpre is the initial preoperative packed cell volume, Hctpost is the packed cell volume on the third postoperative day, and Hctave is the mean of Hctpre and Hctpost. PBV = (K1 × height (m)^3) + (K2 × weight (kg)) + K3, where K1 = 0.3669, K2 = 0.03219, and K3 = 0.6041 for men, and K1 = 0.3561, K2 = 0.03308, and K3 = 0.1833 for women.

Statistical analysis. All analyses were performed using SPSS v19.0 (IBM, USA), and a p-value < 0.05 was considered statistically significant. One-way analysis of variance (ANOVA) with post hoc Bonferroni test was used for normally distributed continuous variables comparison, Kruskal-Wallis analysis with post hoc Nemenyi test was used for skewed continuous variables, and chi-squared test or Fisher's exact test were used for categorical variables comparison. The continuous data were represented by means and standard deviations (SDs) or medians with interquartile ranges, while the qualitative data were represented by frequencies and percentages.

The sample size was calculated using PASS 2011 (NCSS, USA) based on preliminary data and TBL outcome. To detect a difference of 182 ml, 27 patients were required for each group with a power of 90% and an α of 0.05. Considering the loss of follow-up and exclusion, we decided to include at least 30 cases in each group.

Results

A total of 257 patients in our hospital were screened from December 2018 to March 2019 to determine study eligibility. Based on our inclusion and exclusion criteria, 200 eligible patients were eventually included and allocated

Table I. Patient baseline characteristics.

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	Group D (n = 50)	p-value
Mean age, yrs	56.8 (12.4)	55.5 (12.3)	57.9 (13)	58 (11.6)	0.729*
Sex, male/female, n (%)	23/27 (54)	24/26 (52)	28/22 (44)	23/27 (54)	0.763†
Mean BMI, kg/m^2 (SD)	23.18 (3.12)	23.04 (2.9)	24.14 (2.41)	23.33 (2.99)	0.224*
Operated side, left/right, n (%)	25/25 (50)	23/27 (54)	28/22 (44)	26/24 (48)	0.805†
Diagnosis, n (%)					0.906‡
ONFH	19 (38)	21 (42)	23 (46)	24 (48)	
ONFH with osteoporosis	14 (28)	13 (26)	12 (24)	8 (16)	
OA	7 (14)	8 (16)	9 (18)	10 (20)	
OA with osteoporosis	10 (20)	8 (16)	6 (12)	8 (16)	
ASA class, n (%)					0.932†
I	11 (22)	7 (14)	9 (18)	7 (14)	
II	32 (64)	33 (66)	33 (66)	34 (68)	
III	7 (14)	10 (20)	8 (16)	9 (18)	
Mean preoperative values (SD)					
Hb, g/l	133.9 (16.4)	134.1 (15.0)	140.7 (15.4)	134.7 (14.4)	0.081*
Hct, l/l	0.41 (0.04)	0.42 (0.04)	0.43 (0.03)	0.42 (0.03)	0.255*
PLT (× 10^9/l)	210.5 (60.5)	210.4 (70.7)	204.9 (53.5)	196.9 (54.5)	0.637*
INR	1.0 (0.1)	1.04 (0.2)	1.06 (0.2)	1.05 (0.2)	0.375*
PT, s	27.1 (3.7)	27.2 (3.0)	27.7 (3.5)	26.5 (4.2)	0.430*
aPTT, s	11.7 (0.7)	11.9 (0.9)	11.8 (0.9)	11.6 (0.6)	0.216*
D-dimer, mg/l FEU	1.0 (0.8)	1.1 (1.4)	0.8 (0.8)	0.9 (1.0)	0.589*

*One-way analysis of variance.
†Chi-squared test.
‡Fisher's exact test.
aPTT, activated partial thromboplastin time; ASA, American Society of Anesthesiologists; FEU, fibrinogen equivalent unit; Hb, haemoglobin; Hct, haematocrit; INR, international normalized ratio; OA, osteoarthritis; ONFH, osteonecrosis of femoral head; PLT, platelet count; PT, prothrombin time; SD, standard deviation.

into four groups (50 patients in each group) with the assigned intervention (Figure 1). The follow-up time was three months, and no patient was lost to follow-up. There was no significant difference among the four groups with regards to the demographic characteristics and perioperative variables (Table I).

The mean TBL in group D (1,065 ml (SD 318)) was significantly higher than that in group A (605 ml (SD 236)), group B (791 ml (SD 281)), and group C (845 ml (SD 248)), but the mean TBL in group A was significantly lower than that in groups B and C (p = 0.050, one-way ANOVA with post hoc Bonferroni test), However, there was no difference in TBL between groups B and C (p = 1.000, one-way ANOVA with post hoc Bonferroni test) (Figure 2 and Supplementary Table i). Similarly, compared with group D (914 ml (SD 322)), the mean HBL of groups A (453 ml (SD 225)), B (639 ml (SD 282)), and C (695 ml (SD 249)) were significantly reduced (all p < 0.001, one-way ANOVA with post hoc Bonferroni test). The mean HBL of groups B and C was significantly lower than that of group D, but there was no statistically significant difference between groups B and C (p = 1.000, one-way ANOVA with post hoc Bonferroni test) (Figure 2 and Supplementary Table i). The mean Hb reduction of groups A (21.0 g/l (SD 7.8)), B (25.7 g/l (SD 9.4)), and C (27.3 g/l (SD 7.2)) was less than that of group D (32.0 g/l (SD 7.5)) (p < 0.001, p = 0.001, and p = 0.024, respectively, one-way ANOVA with post hoc Bonferroni test). The decrease of Hb level in group A was lower than that in groups B and C, and there was no statistically significant difference between groups B and C (p = 1.000, one-way ANOVA with post hoc Bonferroni test) (Supplementary Table i).

The CRP, interleukin-6 (IL-6), and ESR levels in group D on postoperative day (POD) 1, 2, and 3 were all higher than that in groups A, B, and C, and the difference was statistically significant (p = 0.050, one-way ANOVA with post hoc Bonferroni test). The serum levels of ESR, IL-6, and CRP in group A were lower than those in groups B and C, while there was no significant difference between groups B and C (p = 0.050, one-way ANOVA with post hoc Bonferroni test). There were statistically significant differences in pain scores between groups at each timepoint within two days after surgery (POD 1 and POD 2), and group A had the lowest pain score, however there was no statistically significant difference among the groups on POD 3 (Figure 3). In addition, group A (115° (SD 6°), p < 0.001), group B (109° (SD 5°), p < 0.001), and group C (108° (SD 6°), p = 0.001, all one-way ANOVA with post hoc Bonferroni test) had better results at improving hip flexion than group D (102° (SD 6°)), but there was also a difference in improving hip flexion between group A and group B or between group A and group C (p < 0.001, one-way ANOVA with post hoc Bonferroni test) (Table II).

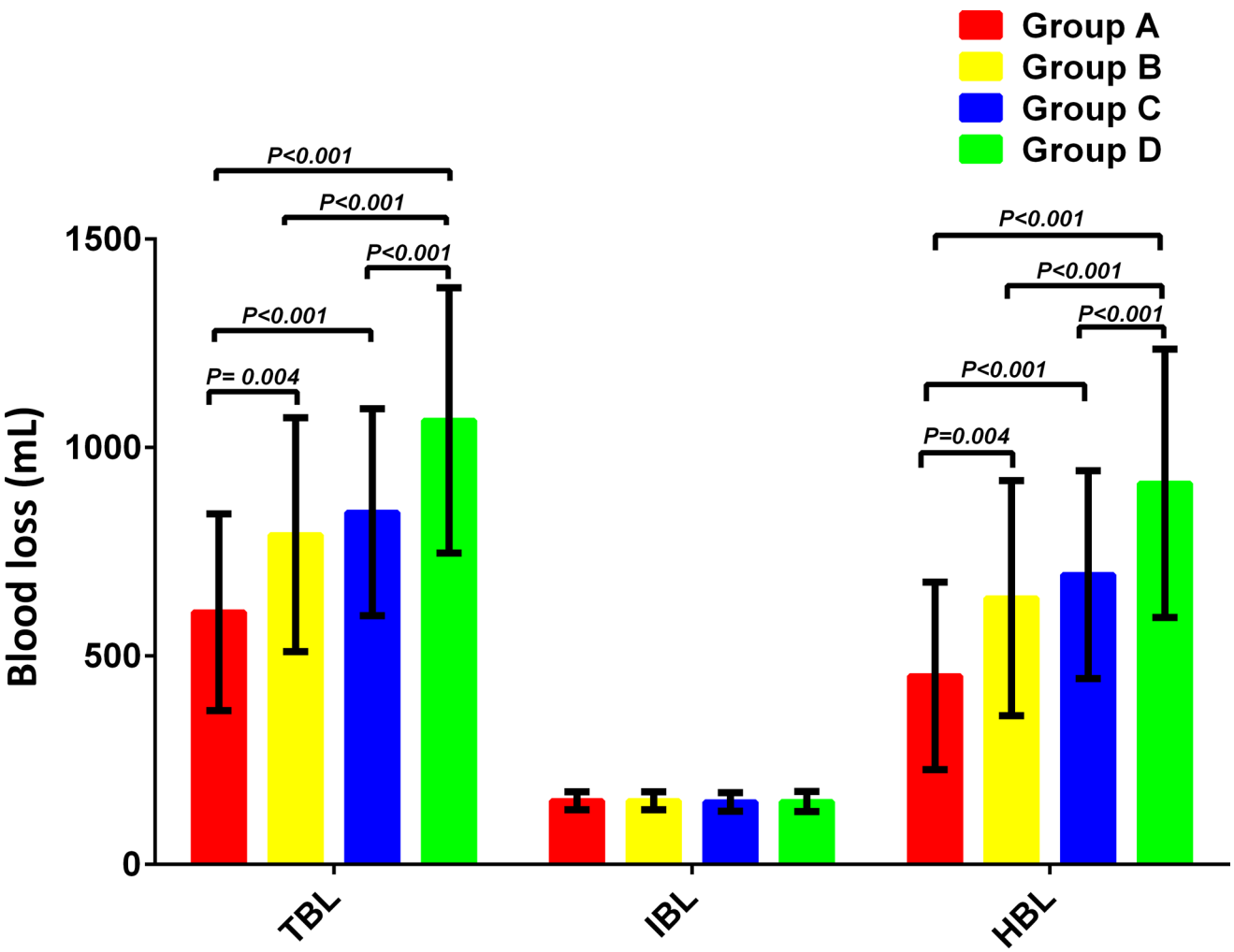

Fig. 2

Graphs showing total blood loss (TBL), hidden blood loss (HBL), and intraoperative blood loss (IBL). A p-value < 0.05 represents significant differences between the groups, and error bars represent ranges.

There was no significant difference between the groups in terms of IBL and LOS.

There we no anemia-related complications during the study. Seven patients (14%) in group D received transfusions due to low Hb concentration. The transfusion rates of groups A, B, and C were significantly lower than that of group D ($p = 0.012$, one-way ANOVA with post hoc Bonferroni test, Table II). Wound leakage was controlled by dressing change and infrared treatment in 14 patients. There was no significant difference among the groups in terms of Harris Hip Scores at three months' follow-up. There was no incidence of PE or DVT and no other significant adverse events were recorded during the three-month follow-up, such as myocardial infarction, stroke, and epilepsy (Table III).

Discussion

In this study, TBL, transfusion rates, postoperative pain, and levels of inflammatory markers were all reduced in the groups receiving CSS during or after THA, compared to placebo. Better hip flexion was also observed. The administration of CSS was not associated with increased VTE rates. In addition, intravenous combined with topical injection of CSS was superior to intravenous or topical injection of CSS alone in reducing perioperative blood loss.

Several studies have reported the efficacy of TXA in reducing blood loss and transfusion in THA patients.[28–31] However, the effect of CSS on blood loss and inflammatory response after THA has yet to be investigated. We found that there is no reported previous study evaluating the haemostatic effect of CSS following THA, although some studies reported that CSS combined with TXA was effective at improving haemostasis after total knee arthroplasty surgery.[18,32,33] Therefore, to our knowledge, this is the first study evaluating perioperative haemostasis and anti-inflammatory effects using CSS and TXA in patients undergoing THA.

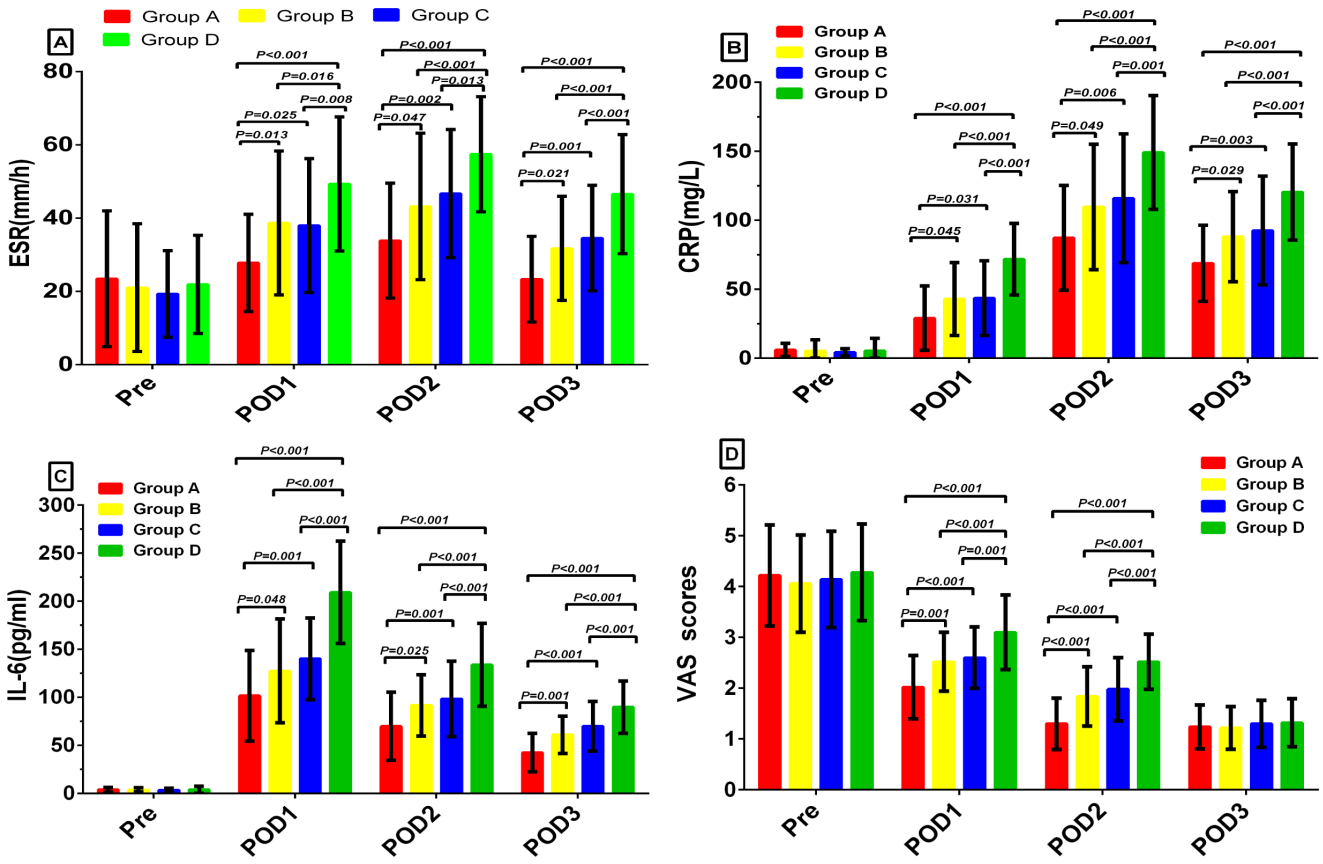

Fig. 3

Mean serum concentration of inflammatory markers in the perioperative period, including a) ESR, b) CRP, and c) interleukin-6 (IL-6). d) Mean longitudinal visual analogue scale (VAS) pain score of each group. POD, postoperative day; Pre, preoperative. A p-value < 0.05 represents significant differences between the groups, and error bars represent ranges.

In this study, we found that the mean TBL of the group without CSS use (Group D) was higher than that of the groups with CSS use (groups A to C), and this might be related to the drug action time of CSS (mean half-life 2.51 (SD 0.95) hours).[18] In addition, 65% of postoperative blood loss occurred within six to eight hours after surgery,[34,35] so the mean TBL in the groups that received CSS was lower than that in the non-used group. Similarly, the mean HBL of the groups that received CSS (groups A to C) was lower than that of the group that did not use CSS (group D), which indicated that TXA combined with CSS was more effective in reducing HBL than the use of TXA alone. HBL often accumulates in the third space such as the joint cavity,[25,36,37] which could cause postoperative inflammation and pain. Therefore, reducing HBL could reduce postoperative inflammation and pain, and that is why inflammatory levels and pain scores were lower in the CSS receiving groups (groups A to C) than the non-CSS receiving group (group D). In this study, pain scores were found to be lower in the groups that used CSS (groups A to C) than the group without CSS (group D) ($p = 0.050$, one-way ANOVA with post hoc Bonferroni test), which suggested that CSS could reduce postoperative pain after THA, similar to the results reported in other studies.[16,33] However, the statistically significant differences in pain scores among the groups did not reach the minimum clinically significant difference (MCID) of 18.6 mm.[38] Therefore, the difference in pain score had no clinical significance.

In this study, intraoperative blood loss was low (about 150 ml) in all four groups, and there was no difference among them. We speculated that this might be because our centre has been committed to the research of enhanced recovery after surgery. During the perioperative period, we adopted careful blood management,[39] including intraoperative blood loss reduction by optimizing surgical techniques, controlling hypotension, and using TXA. Therefore, with the above measures, the intraoperative blood loss in this study was relatively low. In addition, the results of intraoperative blood loss in this study were consistent with those reported in other studies.[40,41]

The clinical consequences that were caused by inflammatory response depends on the degree of the inflammatory response.[42] Adequate inflammatory response could repair tissue damage, but excessive and persistent

Table II. Perioperative outcomes. For the p-values, P1 = differences between the four groups; P2 = A vs B; P3 = A vs C; P4 = A vs D; P5 = B vs C; P6 = B vs D; P7 = C vs D.

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	Group D (n = 50)	p-value*						
					P1	P2	P3	P4	P5	P6	P7
Mean operating time, mins (SD)†	60 (10)	60 (12)	60 (13)	62 (12)	0.634	1.000	0.999	0.694	0.997	0.668	0.785
Transfusion rate, n (%)‡	0 (0)	0 (0)	0 (0)	7 (14)	< 0.001	N/A	N/A	0.012	N/A	0.012	0.012
Preop hip function†											
Mean flexion, ° (SD)	90 (20)	91 (20)	89 (21)	92 (20)	0.869	0.969	1.000	0.927	0.946	0.998	0.891
Mean abduction, °(SD)	24 (8)	23 (9)	23 (8)	23 (7)	0.905	0.970	0.926	1.000	0.998	0.977	0.937
Postop hip function†											
Mean flexion, ° (SD)	115 (6)	109 (5)	108 (6)	102 (6)	< 0.001	< 0.001	< 0.001	< 0.001	1.000	< 0.001	0.001
Mean abduction, ° (SD)	36 (3)	37 (3)	36 (3)	37 (3)	0.347	0.551	0.999	0.503	0.646	1.000	0.599
Mean preop HHS, points (SD)†	39 (14)	39 (14)	39 (14)	39 (14)	0.322	0.998	0.957	0.560	0.897	0.681	0.269
Mean postop HHS, points (SD)†	88 (11)	88 (10)	88 (11)	87 (12)	0.079	0.948	0.724	0.064	0.959	0.211	0.469
Mean LOS, days (SD)§	5 (2)	5 (2)	5 (2)	5 (2)	0.151	0.130	0.940	0.370	0.240	0.830	0.570

*Refers to the difference between the groups.
†One-way analysis of variance with post hoc Bonferroni test.
‡Chi-squared test.
§Kruskal-Wallis analysis with post-hoc Nemenyi test.
HHS, Harris Hip Score; LOS, length of hospital stay; N/A, not applicable; SD, standard deviation.

Table III. Complications.

Variable	Group A (n = 50)	Group B (n = 50)	Group C (n = 50)	Group D (n = 50)	p-value
Stroke	0	0	0	0	N/A
Deep infection	0	0	0	0	N/A
Wound complications	3	4	5	2	0.792*
Superficial wound necrosis	0	0	0	0	N/A
DVT	0	0	0	0	N/A
PE	0	0	0	0	N/A
Superficial infection	0	0	0	0	N/A
IMVT	4	6	4	5	0.951†
Epilepsy	0	0	0	0	N/A
Myocardial infarction	0	0	0	0	N/A

*Fisher's exact test.
†Chi-squared test.
DVT, deep-vein thrombosis; IMVT, intramuscular venous thrombosis; N/A, not applicable; PE, pulmonary embolism.

inflammation would lead to adverse consequences, such as pain, vomiting, and other complications.[43] Therefore, measures should be taken to suppress this excessive and persistent inflammatory response. In this study, we found that the secretion levels of IL-6, CRP, and ESR were decreased in the groups that used CSS (groups A to C) compared with the group that did not use CSS (group D). These results suggested that CSS might have an anti-inflammatory effect. In addition, the combined use of TXA with CSS reduced TBL and the level of inflammatory factors, which might play an important role in reducing inflammation and surgical trauma.[44,45] Additionally, CSS reduced the increase of capillary permeability, which led to a reduction in the secretion of inflammatory factors. Although there are different opinions about the correlation between inflammatory factor levels and clinical outcomes,[44–46] significant differences in inflammatory factor levels between groups are also reflected in clinical outcomes such as pain score and range of motion (ROM).

In this study, we found that groups A, B, and C were superior to group D in terms of hip flexion, with group A having the best effects. Furthermore, previous studies

showed that in order to ensure the difference in ROM is not due to performance changes between measurements, the range of difference required is approximately 10°.[47] There was no statistically significant difference in hip flexion among the groups in this study except group A. Therefore, it is unclear whether this difference is clinically relevant. In this study, there was no significant difference in VTE among the four groups. In addition, peak coagulation and fibrinolysis parameters did not increase in the CSS groups (groups A to C) compared with the non-CSS group (group D) (Supplementary Figure a), which indicated that the use of CSS had no effect on coagulation and fibrinolysis.

The main limitation of this study was the exclusion of patients with high risk of cardiovascular and cerebrovascular diseases and thromboembolic episodes. Therefore, they cannot benefit from our guidelines. Secondly, the follow-up length of this study might be considered short (three months); however, it is sufficient to observe the associated adverse events, as both TXA and CSS have a biological half-life of three hours, 90% of which are excreted within 24 hours. Thirdly, the estimates of blood loss are based primarily on Hct values on day 3 postoperatively. If the patients are discharged from hospital before the fifth day after surgery, there is a risk that haemodilution would lead to inaccurate estimation of blood loss,[48] but there is no significant difference in length of stay among the four groups. We believed that the possible inaccuracies resulting from haemodilution do not alter the clinical significance of the results. Therefore, the estimate of blood loss was correct and valid. Finally, there was a selection bias of the type of hip joint diseases that were included in this study, and other hip joint diseases such as rheumatoid arthritis and traumatic arthritis were excluded. Therefore, these results cannot be applied to all hip joint disorders.

In conclusion, our study showed that patients receiving CSS additionally to TXA had less perioperative blood loss, less postoperative hip pain, lower transfusion rates, lower levels of inflammatory cytokines, and better early hip flexion following THA without an increase in the associated VTE events. In addition, intravenous combined with topical injection of CSS was superior to intravenous or topical injection of CSS alone in reducing perioperative blood loss.

Supplementary material

Perioperative blood loss, coagulation, and fibrinolysis parameters were analyzed along with p-values and correction p'values of perioperative outcome indicators.

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